REMARKS

Claims 24-39 were pending. The Examiner has indicated that claims 24-29 are in condition for allowance. Claims 33, 35-37, and 39 are cancelled. Claims 34 and 38 are amended. No new subject matter is introduced.

Interviews

Applicants' representative wishes to thank the Examiner for the opportunity to discuss the Office Action in two telephone interviews which took place on April 23, 2003, and April 25, 2003. The rejection of claims 30-39 under 35 U.S.C. 112, first and second paragraphs, was discussed in the April 23, 2003, interview, without reaching agreement. The Examiner asked for a follow-up interview after she had time to consider the claims further. The rejection of claims 30-39 under 35 U.S.C. 112, first and second paragraphs, was discussed again in the April 25, 2003, interview, with some clarification of issues and agreement by the Examiner to consider a draft response. Additional issues relating to the declaration and an Information Disclosure Statement were also discussed in the April 23, 2003, interview (see below).

Declaration

The Examiner indicated on the Office Action Summary Sheet that no declaration has been submitted. Applicants submitted a declaration executed by all three named inventors on February 18, 2000, as part of a response to a Notification of Missing Requirements Under 35 U.S.C. 371. Applicants received a return postcard stamped by the USPTO indicating the declaration was received by the USPTO on February 22, 2000. A copy of the response to the Notification of Missing Requirements Under 35 U.S.C. 371, including a copy of the executed declaration, and the return postcard, is enclosed herewith.

Information Disclosure Statements

In the telephone interview with the Examiner on April 23, 2003, Applicants' representative advised the Examiner that an Information Disclosure Statement (IDS) filed with the request for entry into the United States on July 23, 1999, does not appear to have been checked off in any Office Communication. At the request of the Examiner, Applicants sent a copy of the IDS and Form 1449 filed July 23, 1999, to the Examiner by facsimile on April 24, 2003. The Examiner indicated in the telephone interview that she would attempt to locate the references that accompanied the IDS as it was originally filed. Applicants request the Examiner to contact Applicants' representative by telephone if she requires replacement copies of the references cited in the IDS.

Withdrawn Rejections and Objections

Applicants gratefully acknowledge withdrawal of the following objections and rejections:

Objection of claims 4-22 under 37 CFR 1.75(a), withdrawn in light of Applicants' amendments filed September 26, 2000.

Rejection of claims 19-22 under 35 U.S.C. 101, withdrawn in light of Applicants' amendments filed September 26, 2000.

Rejection of claims 9, 12, 15, 18, 19-22 under 35 U.S.C. 112, second paragraph, withdrawn in light of Applicants' amendments filed September 26, 2000.

Rejection of claims 1-18 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, withdrawn in light of Applicants' amendments filed September 26, 2000.

Rejection of claims 1-6, 9, 11, 12, 16, 17, 19 and 20 under 35 U.S.C. 102(e) as being anticipated by Henderson, withdrawn in light of Applicants' amendments filed September 26, 2000.

Rejection of claim 23 under 35 U.S.C. 102(e) as being anticipated by Watson, withdrawn in light of Applicants' amendments filed September 26, 2000.

Rejection of claims 8, 10, 13-15 and 18 under 35 U.S.C. 103(a) as being unpatentable over Henderson and further in view of Davis, withdrawn in light of Applicants' amendments filed September 26, 2000.

Rejection of Claims 33-39 Under 35 U.S.C. 112, Second Paragraph

The Examiner rejected claims 33-39 under 35 U.S.C. 112, second paragraph, for allegedly failing to particularly point out and distinctly claim the subject mater which the applicant regards as the invention. Specifically, the Examiner requests clarification of which polynucleotides confer each of the various biological effects recited in claim 33. In support of her position, the Examiner contends that at least certain of the biological effects are mutually exclusive. According to the Examiner, the claim is thus unclear because no one polynucleotide will have all of the effects, and it is unclear which sequence is associated with which effect.

In the telephone interview conducted April 25, 2003, the Examiner indicated the rejection could be overcome with separate claims drawn to specific oligonucleotides and their specific effects.

Applicants, in response, are of the view that the Examiner's rejection of claims 33-39 under 35 U.S.C. 112, second paragraph, is inconsistent with the Examiner's treatment of claim 30, from which claims 33-39 depend. Applicants respectfully point out that the Examiner appears to accept use of the term "modulating an immune response" as used in claim 30. Claim 33, which depends from claim 30, recites various specific biological effects and in so doing merely further specifies various embodiments of the term "modulating an immune response". Some of the various embodiments involve immune stimulation, and others involve immune inhibition. Applicants and the Examiner thus appear to agree that "modulating an immune response" can encompass both immune stimulatory and immune inhibitory effects. Applicants are therefore of the view that the Examiner's rejection of claims 33-39 under 35 U.S.C. 112,

second paragraph, is inconsistent with the Examiner's treatment of claim 30, from which claims 33-39 depend.

Notwithstanding the foregoing, Applicants, for the purpose of expediting prosecution, have cancelled claims 33, 35-37, and 39; amended claim 34 to incorporate the limitations of claim 35; and amended claim 38 to incorporate the limitations of claim 39. Claim 34 as amended associates specific polynucleotides with inducing a cytolytic T lymphocyte response. Support for this claim can be found, inter alia, in Example 5. Claim 38 as amended associates specific polynucleotides with inducing a Th1 immune response. Support for this claim can be found, inter alia, in Examples 4 (induction of IgG2a) and 9 (suppression of *L. major* by IL-12p40 (SEQ ID NO:10)). Example 9 and Figure 7 illustrate induction of Th1 to such an extent as to overcome infection by *L. major* because BALB/c mice generally are susceptible to *L. major* due to their inability to mount an effective Th1 response.

Because it is believed that the amendments to the claims fully overcome the rejection of claims 33-39 under 35 U.S.C. 112, second paragraph, Applicants respectfully request the Examiner to withdraw the rejection.

Rejection of Claims 30-39 Under 35 U.S.C. 112, First Paragraph

The Examiner has rejected claims 30-39 under 35 U.S.C. 112, first paragraph, for alleged lack of enablement. Applicants note that the Examiner has indicated that the specification is enabling for modulating immune responses in BALB/c mice following in vivo administration of a polynucleotide and ovalbumin. The Examiner's rejection appears to rest on an alleged failure to provide any particular guidance for the successful induction of a cytolytic T lymphocyte response, induction of Th2 and Th1 immune responses, breaking immune tolerance, regulating Th1/Th2 helper cell responses, switching immunoglobulin classes, treating any and/or all autoimmune diseases and/or induction of tolerance comprising the in vivo administration (via any route) of any antigen in combination with any oligonucleotide listed in claim 30. For the reasons provided below, Applicant respectfully disagrees with the rejection.

General Remarks. Without meaning to cede to any of the Examiner's reasons for making the rejection, it is pointed out that claims 33, 35-37, and 39 have been cancelled; claim 34 has been amended to incorporate the limitations of claim 35; and claim 38 has been amended to incorporate the limitations of claim 39. These claim amendments aside, Applicants believe the specification is enabling to a person skilled in the art to which it pertains for all the cited purposes. For example, a person skilled in the art would understand that mouse models are the basis for innumerable clinical trials of new pharmaceutical agents. In addition, a person of skill in the art would understand that agents that induce a Th1 immune response will generally be expected to be useful in inducing a cytolytic T lymphocyte response, breaking immune tolerance, regulating Th2 immune responses, switching immunoglobulin classes (e.g., toward IgG2a and away from IgG1 and IgE in mice, and treating certain autoimmune diseases. Furthermore, a person of skill in the art would understand that agents that induce a Th2 immune response will generally be expected to be useful in regulating Th1 immune responses, switching immunoglobulin classes (e.g., toward IgG1 and IgE), treating certain autoimmune diseases, and inducing tolerance. These general considerations, in combination with literal support for each

and every embodiment, thus support a conclusion that, contrary to the Examiner's assertion, the specification is enabling for the full scope of the claimed subject matter.

We now address each of three factors cited by the Examiner in support of the rejection.

1. State of the Prior Art and Predictability or Unpredictability of the Art. The Examiner supports her rejection in part by citing references for the proposition that gene therapy, antisense, and immunotherapy are highly unpredictable. The Examiner's reliance on these references is misplaced, however, because the instant claimed invention does not involve or require gene therapy or antisense. With respect to immunotherapy, the Examiner recites a passage from the concluding paragraph of Weiner (*J Leukoc Biol* 68:455-462 (2000)) regarding areas for further study in the field of immunostimulatory CpG oligodeoxynucleotides. In response, Applicant points out to the Examiner that not all the instantly claimed polynucleotides are immunostimulatory CpG oligodeoxynucleotides (refer, for example, to SEQ ID NOs 17, 20, and 21, all without a CG dinucleotide). Furthermore, Applicants point out that the third full paragraph in the right hand column on page 457 of Weiner includes the passage, "Studies in humans are only now beginning. However, extensive studies have been done in rodents, and some studies have been done in non-human primates. The observed in vivo data fits well with the in vitro data outlined above." [Emphasis added.] Thus Applicants believe the Examiner's reliance on this first factor is misplaced because it either does not apply or it is inconsistent with the teachings of the art cited by the Examiner.

2. Amount of Direction or Guidance Presented in the Specification and the Presence or Absence of Working Examples. The Examiner appears to suggest that the specification teaches only modulation of immune responses in BALB/c mice comprising intraperitoneal administration of ODN 1668 and ovalbumin. Applicants respectfully point out that the specification teaches much more than suggested by the Examiner. For example, Example 3 includes both intravenous and intraperitoneal injection with oligonucleotide CRE (SEQ ID NO:8). Example 4 and associated Figure 3 describe intramuscular or subcutaneous (footpad) injection into C57/B6 mice of seven oligonucleotides, other than ODN 1668. This example clearly demonstrates induction of Th1-associated IgG2a immunoglobulin induction. Example 5 and Figures 1and 2 deal with CTL responses to ovalbumin protein or K^b restricted ovalbumin peptide SIINFEKL plus fifteen oligonucleotides, other than ODN 1668. This example clearly addresses induction of a cytolytic T lymphocyte response. Example 8 deals with control of syngeneic tumor in DBA mice involving treatment with oligonucleotide and tumor cells as antigen. This example thus demonstrates breaking tolerance. Example 9 deals with control in BALB/c mice of infection with *L. major*. BALB/c mice ordinarily are susceptible to infection with *L. major* because they fail to mount an effective Th1 response. This example thus clearly demonstrates the ability of IL-12p40 (closed squares in Fig. 7; SEQ ID NO:10) to induce a Th1 response. Thus Applicants believe the Examiner's reliance on this second factor is misplaced because the specification teaches much more than the Examiner acknowledges.

3. Breadth of the Claims and Quantity of Experimentation Required. The Examiner alleges that since the specification fails to provide any particular guidance for the successful induction of a cytolytic T lymphocyte response, induction of Th2 and Th1 immune responses, breaking immune tolerance, regulating Th1/Th2 helper cell responses, switching

immunoglobulin classes, treating any and/or all autoimmune diseases and/or induction of tolerance comprising the in vivo administration (via any route) of any antigen in combination with any oligonucleotide listed in claim 30 in any organism, and since determination of the factors required such in vivo success is highly unpredictable, it would require undue experimentation to practice the invention over the broad scope claimed. The Examiner further alleges that the quantity of experimentation required to practice the invention as claimed would require the de novo determination of accessible target sites, modes of delivery and formulations to target appropriate cells and/or tissues in vivo whereby treatment the various immunomodulatory effects are provided. Applicants respectfully disagree. The claims currently under examination are drawn to but a few specific sequences. Furthermore, in addition to the rebuttals raised above in addressing the first and second factors, Applicants point out passages in the specification that teach how to make and use the claimed polynucleotides. These passages include, without limitation, page 10, second full paragraph (dosing); and page 15, second full paragraph – page 16, third full paragraph (formulation and routes of administration). In addition, those of skill in the art will recognize that administration to cells of the immune system can be accomplished via any of a number of possible routes of delivery, including direct local injection (e.g., into a tumor), systemic administration, and mucosal administration. Thus Applicants believe the Examiner's reliance on this third factor is misplaced because the claims are not overly broad and the amount of experimentation required is no more than routine in the relevant art.

In view of the foregoing, Applicants respectfully request the Examiner to withdraw her rejection of claims 30-39 under 35 U.S.C. 112, first paragraph.

Summary

Applicants have amended claims 34 and 38 and cancelled claims 33, 35-37, and 39 for the sole purpose of speeding prosecution. Applicants request withdrawal of the rejection of claims 33-39 under 35 U.S.C. 112, second paragraph, in view of the amendments and arguments set forth above. Applicants likewise request withdrawal of the rejection of claims 30-39 under 35 U.S.C. 112, first paragraph, in view of the amendments and arguments set forth above.

It is believed that the claims are in condition for allowance. A favorable and early response is earnestly solicited. Should the Examiner have any questions, she is requested to call Applicants' representative at the number shown below.

Respectfully submitted,

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Appendix to Amendment Showing Marked-Up Claims

34. (Amended) [The method of claim 30] A method of inducing a cytolytic T lymphocyte response, comprising

contacting an immune cell with an antigen and at least one polynucleotide, wherein the polynucleotide comprises a sequence of a binding site for a transcription factor and which is chosen from

GATTGCCTGACGTCAGAGAG (SEQ ID NO:8),
GGAATGACGTTCCCTGTG (SEQ ID NO:9),
TCGATCGGGGCGGGGCGAGC (SEQ ID NO:12),
GTCCATTTCCCGTAAATCTT (SEQ ID NO:16),
CTGATTTCCCCGAAATGATG (SEQ ID NO:19),
GTATTTCCCAGAAAAGGAAC (SEQ ID NO:21),
AAGCGAAAATGAAATTGACT (SEQ ID NO:22), and
CAGGCATAACGGTTCCGTAG (SEQ ID NO:23),

wherein the polynucleotide is capable of inducing a cytolytic T lymphocyte response.

38. (Amended) [The method of claim 30] A method of inducing a Th1 immune response, comprising

contacting an immune cell with an antigen and at least one polynucleotide, wherein the polynucleotide comprises a sequence of a binding site for a transcription factor and which is chosen from

GATTGCCTGACGTCAGAGAG (SEQ ID NO:8),
AGCTATGACGTTCCAAGG (SEQ ID NO:10),
TCGATCGGGGCGGGGCGAGC (SEQ ID NO:12),
AGCGGGGGCGAGCGGGGGCG (SEQ ID NO:14),
GTCCATTTCCCGTAAATCTT (SEQ ID NO:16),
CTGATTTCCCCGAAATGATG (SEQ ID NO:19),
AAGCGAAAATGAAATTGACT (SEQ ID NO:22), and
CAGGCATAACGGTTCCGTAG (SEQ ID NO:23),

wherein the polynucleotide is capable of inducing a Th1 immune response.